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(54) Title: A GEL-FORM PHARMACEUTICAL PREPARATION

(57) Abstract

The invention relates to a pharmaceutical formulation which contains a corticosteroid and a solvent. According to the invention the formulation is brought to gel form by using a gellant which is a hydroxyalkyl cellulose, in particular hydroxyethyl cellulose or hydroxypropyl cellulose.

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A GEL-FORM PHARMACEUTICAL PREPARATION

The invention relates to a corticosteroid-containing pharmaceutical preparation intended for topical use.

Corticosteroids constitute a large group of compounds with a pregnene or pregnadiene backbone and with versatile medical uses. In particular they are used topically as anti-inflammatory dermatological medicines. Examples of corticosteroids on the market include hydrocortisone, dexamethasone, betamethasone, methylprednisolone, prednisolone, prednisone, beclomethasone, fludrocortisone, triamsinolone, desonide, fluprednidene, clobetasone, alclomethasone, momethasone, desoxymethasone, fluosinonide, budesonide and fluosinolone.

Common forms of preparations include solutions, ointments, creams and liniments. Certain ester-form glucocorticoids, such as betamethasonide propionate, have also been prepared as a gel in which Carbomer, i.e. carboxyvinyl polymer, has been used as the gellant.

Hydrocortisone gels are not available on the market. Attempts to prepare a hydrocortisone gel by using conventional gellants such as Carbomer polymer have failed owing to the poor stability of hydrocortisone.

We have now observed, surprisingly, that by using hydroxyalkyl cellulose, in particular hydroxyethyl cellulose, as the gellant, very stable corticosteroid gels are obtained.

The characteristics of the invention are given in Claim 1.

A corticosteroid-containing pharmaceutical formulation according to the invention is characterized in that the

formulation has been brought to gel form by means of a gellant, the gellant being hydroxyalkyl cellulose.

The corticosteroid may be any pharmaceutically acceptable corticosteroid. Preferably the corticosteroid is hydrocortisone.

According to a preferred embodiment, the hydroxyalkyl cellulose used as the gellant is hydroxyethyl cellulose or hydroxypropyl cellulose, in particular hydroxyethyl cellulose.

The solvent used is preferably a mixture of water and a lower alcohol, such as ethanol or propanol. A mixture of water and ethanol or of water and isopropanol is especially preferable.

Glycerol or propylene glycol is preferably added to the formulation in order to prevent skin drying caused by the alcohol (ethanol). For this purpose it is also possible to add some oil component, such as Cetiol SN (cetearyl-isononanoate). It is also possible to add suitable perfumes and preservatives. Examples of suitable preservatives include methylparahydroxybenzoate, propyl-parahydroxybenzoate and benzyl alcohol.

The invention is described in greater detail with the help of the following, non-limiting examples.

Example 1

Hydrocortisone gels in which hydroxyethyl cellulose (HEC) is used as the gellant

Four hydrocortisone-containing gel batches I, II, III and IV were prepared. Batches I and II were prepared on a laboratory scale (1000 g/batch) and batches III and IV were prepared on an industrial scale (150 kg/batch). The soft

gels were packed into polyethylene tubes. The stability of the gels was monitored for 18 months (batch I), 12 months (batch II) and 3 months (batches III and IV). The gels were prepared as follows: HEC was added to a mixture of water and ethanol (containing only a portion of the ethanol) while stirring, and the mixture was allowed to gel. Thereafter the glycerol was added while stirring. The balance of the ethanol was added while stirring. Thereafter the active ingredient was added to the gel while stirring.

Gel compositions (mg/g):

	Batches I, III and IV	Batch II
Hydrocortisone	10.00	10.00
Hydroxyethyl cellulose	15.00	15.00
Glycerol (99.5 %)	60.00	-
Ethanol (96 %)	500.00	500.00
Purified water	415.00	475.00

Stability tests:

The batches were stored at a relative humidity of 60 %. The temperature was 25 °C (batches I, III and IV) and respectively 20 °C (batch II).

According to the objective, the amount of degradation products may be at maximum 5 %, the amount of hydrocortisone should be 9.0 - 11.0 mg/g, and the pH should be 5 - 8.5.

Results:

Batch I

Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
Beginning of test	0.6	10.2	7.5
3 months	0.7	10.1	5.8
7 "	2.3	10.1	5.7
12 "	1.9	10.1	5.7
18 "	1.9	9.5	5.7

Batch II

Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
Beginning of test	*)	*)	*)
12 months	2.2	10.3	5.6

*) not determined

Batch III

Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
Beginning of test	0.6	10.3	6.6
3 months	0.7	9.8	6.8

Batch IV

Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
Beginning of test	0.55	10.2	7
3 months	0.8	10.2	7

The results show that all of the batches remained well within the guideline values as regards hydrocortisone concentration, hydrocortisone degradation products and pH.

Example 2

Hydrocortisone gels in which Carbomer or Stabileze polymer was used as the gellant

For the sake of comparison, four hydrocortisone gel formulations A, B, C and D were prepared, in which the gellant used was carboxyvinyl polymer Carbomer 980 or Carbomer 940, or polymer Stabileze^{R} QM, which is a copolymer of methylvinyl ether and maleic acid anhydride, cross-bridged with 1,9-decadiene. These gellants yield a very low pH value (the pH of a 1 % aqueous dispersion of Carbomer polymer is 2.5 - 3.0), and therefore sodium hydroxide was added to adjust the pH to the desired range. The auxiliary compositions and hydrocortisone concentrations of the preparations are shown in Table 1, which also shows the stabilities of the preparations.

Table 1 shows that, already after three months of storage, a large quantity of degradation products of hydrocortisone had formed. After six months of storage the concentration of hydrocortisone degradation products in preparations A, B and D clearly exceeded the guideline values (guideline value at maximum 5 %), and the concentration of degradation products in preparation C was also very high (4 %).

The examples given above clearly show that highly stable hydrocortisone gels are obtained by using hydroxyethyl cellulose as the gellant. Although test results have not been presented, it can be assumed that corresponding results would be obtained also with respect to other corticosteroids and when using other hydroxyalkyl celluloses, in particular hydroxypropyl cellulose.

Table 1

Auxiliary composition		A	B	C	D
Carbomer 980		1.0 %	1.0 %	-	-
Carbomer 940		-	-	1.0 %	-
Stabileze QM		-	-	-	1.0
Ethanol 96 %		60.0 %	60.0 %	60.0 %	27.0 %
Sodium hydroxide		0.06 %	0.06 %	0.015 %	0.135 %
Macrogol 400		3.0 %	3.0 %	-	-
Glycerol		10.0 %	8.0 %	10.0 %	-
Propylene glycol		-	-	-	27.0 %
Purified water		24.94 %	26.84 %	27.98 %	43.9 %
Sodium medetate		-	0.1 %	-	-
Initial value	Hydrocortisone concentration	10.1 mg/g	10.2 mg/g	10.1 mg/g	10.7 mg/g
	Degradation products	none	1.7 %	1.1 %	1.4 %
3 months	Hydrocortisone concentration	9.1 mg/g	9.7 mg/g	10.3 mg/g	9.8 mg/g
	Degradation products	6 %	6 %	2.9 %	4 %
6 months	Hydrocortisone concentration	9.2 mg/g	9.1 mg/g	9.5 mg/g	9.2 mg/g
	Degradation products	10 %	7 %	4 %	11 %

The above embodiments of the invention are only examples of the implementation of the idea of the invention. For a person skilled in the art it is clear that the various embodiments of the invention may vary within the claims presented below.

CLAIMS

1. A pharmaceutical formulation comprising a corticosteroid and a solvent, characterized in that the formulation has been brought to gel form by using a gellant, the gellant being a hydroxyalkyl cellulose.

2. A formulation according to Claim 1, characterized in that the corticosteroid is hydrocortisone.

3. A formulation according to Claim 1 or 2, characterized in that the hydroxyalkyl cellulose is hydroxyethyl cellulose or hydroxypropyl cellulose.

4. A formulation according to Claim 1, 2 or 3, characterized in that the solvent is a mixture of water and a lower alcohol.

5. A formulation according to any of the above claims, characterized in that the corticosteroid is hydrocortisone, the gellant is hydroxyethyl cellulose, and the solvent is a mixture of water and ethanol.

6. A formulation according to Claim 5, characterized in that it additionally contains glycerol.

7. A formulation according to Claim 5 or 6, characterized in that it additionally contains propylene glycol.

8. A formulation according to Claim 5, characterized in that it contains approx. 0.1 % by weight hydrocortisone and 1 - 2 % by weight hydroxyethyl cellulose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/01000

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/56, A61K 9/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 8809174 A1 (SCHERING CORPORATION), 2 December 1988 (02.12.88) --	1-8
X	US 5110809 A (JONAS WANG ET AL), 5 May 1992 (05.05.92) --	1-8
X	US 4267173 A (RICHARD W. DRAPER), 12 May 1981 (12.05.81), See especially Formulation 10 --	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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02/03/99

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